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OFFICE OF NAVAL RESEARCH

ANNUAL PROGRESS REPORT

and

PROPOSAL FOR RENEWAL OF CONTRACT

Report prepared by: José M.R. Delgado, M.D.   Date: January 30, 1957

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CONTRACTOR: Yale University

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TITLE OF PROJECT: NEUROLOGICAL MECHANISMS IN EPILEPSY AND IN GROUP BEHAVIOR

Objectives: a) To study in awake animals the neurological mechanisms involved in the onset, spread and clinical manifestations of epilepsy.

b) Influence of cerebral stimulation on group behavior of animals recorded by time-lapse photography.

ABSTRACT OF RESULTS

A. Since Start of Project

1. Learning Motivated by Electrical Stimulation of the Brain. In cats the emotional disturbance induced by electrical stimulation of specific cerebral structures might be used to motivate learning. It has been demonstrated that fear-like reactions elicited by direct cerebral stimulation has all the drive properties of a true emotion: a) it could be used to establish conditioned response; b) it could motivate the trial and error learning and performance of an instrumental response; c) it could be used to condition an emotional disturbance to a distinctive compartment from which the animals learned to escape; d) it could serve as a punishment to teach hungry animals to avoid food.

2. Functional Correlation Between Motor Cortex and Cerebellum. Two systems seem to exist in the cerebellum. One with a lower threshold, responsible for coordinated motor responses upon stimulation, and another with a higher threshold able to elicit facilitory and inhibitory effects. Electrical stimulation of the cerebellum induced lasting changes in the electrical activity of the cerebral motor cortex. However, no changes in excitability were found. Ablation experiments and simultaneous stimulation of motor cortex or cerebellum showed a considerable functional independence of both areas. Cerebellar stimulation was able to evoke motor activity similar to that evoked by stimulation of the cerebral motor area.

3. Cerebral Structures Involved in Transmission and Elaboration of Noxious Stimulation. Pathways for nociceptive sensory integrations were investigated in monkeys. The following structures seemed to be related to pain perception: lateral part of the tegmentum, central gray, posteroventral nucleus of the thalamus, crus of the fornix and the posterior part of the hippocampus. Other areas of the brain, including the sensory and motor cortex, seemed to be excluded from the system.

4. Influence of Various CO_2 Concentrations on Electrical Activity and Excitability of the Brain in the Waking Monkey. Threshold of electrical stimulation of the hypothalamus and reticular formation decreased under 10 per cent, 15 per cent and 30 per cent CO_2. The electrical activity of the motor cortex, occipital cortex, thalamus and reticular substance was modified after CO_2 exposure. The hypothalamus was less affected.

5. Evaluation of Permanent Implantation of Electrodes within the Brain. Study of the brain of 75 cats and 63 monkeys in which electrodes were implanted for 1 to 14 months showed that prolonged electrical stimulation of the brain did not cause modifications of thresholds, variation of spontaneous electrical activity or detectable local histological changes. A critical evaluation of results of electrical stimulation and electrical recordings was made.

6. Convulsive Activity Evoked by Cerebral Stimulation in the Awake Monkey. The motor cortex had the lowest convulsive threshold, convulsive movements were usually localized and electrical afterdischarges spread over a wide area. The premotor cortex had somewhat higher thresholds with more motor spreading. The frontal cortex had still higher convulsive thresholds and the occipital cortex had the highest. The duration of afterdischarges was longest from motor and premotor cortex, shorter from frontal, and shortest from occipital cortex. Of the deep structures, the hippocampus had the lowest convulsive threshold. Lowering of convulsive thresholds and increased tendency toward spreading could be observed when an area was repeatedly stimulated for long periods with intensities producing convulsive afterdischarges.

7. Lasting Effects on Behavior Evoked by Cerebral Stimulation of the Cat. Social behavior was recorded continuously for 10 hours daily by time-lapse photography. Electrical stimulation of the amygdaloid complex produced considerable increase in frequency and time spent in nuzzling, sniffing, licking, rubbing, and also an increase in "playful" activity.

B. During Current Report Period

Summary of published work and papers accepted for publication follows:

1. Electrical Stimulation of Monkey Brain with Various Frequencies and Pulse Durations. Effects of altering the duration and frequency of pulses upon the threshold of motor and autonomic responses produced by electrical stimulation of different cortical and subcortical areas of the brain were studied in unanesthetized monkeys with permanently implanted electrodes. Pulses of 0.01-5.0 msec. duration, and frequency ranges of 10-5000 cycles/sec. were used. Voltage and current of stimuli passing through the animal were simultaneously monitored and measured by a dual channel cathode-ray oscilloscope. The following conclusions were derived from the experimental results: 1) Voltage/current ratio was the same before and after the implantation of electrodes, indicating that prolonged contact with organic tissue does not significantly change the electrical properties of the electrode. 2) Pulse durations of 0.1-0.5 msec. were generally most effective in evoking both motor and autonomic responses. 3) The lowest threshold for both motor and autonomic responses occurred at frequencies of 100-250 cycles/sec. At higher frequencies a sharper increase in threshold values was observed in the case of autonomic responses. In most of the areas studied variation in frequency of stimuli resulted in change of the type of evoked motor responses. At low frequencies (up to 30 cycles/sec.) single contractions followed the rate of stimuli; at higher frequencies (60-500) smooth movements occurred; at very high frequencies (1000-5000) quick, jerky movements at onset of stimulation were observed. Similar fundamental changes, and at approximately the same critical frequencies, were obtained from different, widely separated areas of the gray and white matter of both cortical and subcortical areas of the brain.

2. Attraction and Avoidance Evoked by Septal and Rhinencephalic Stimulation in the Monkey. In a group of 6 monkeys permanent multilead electrodes

were implanted in septum pellucidum, amygdala, fornix and other cerebral structures. By means of a belt and chain each animal was tested for 1-2 hours daily on a rectangular table around which it could move freely. The points of the brain tested at random were electrically stimulated only when the monkey was on one side of the table. The sides were altered at random. Excitation consisted of unidirectional rectangular pulses, 100 cycles/sec., 0.24 msec. of pulse duration, 0.8-1.0 milliamps., applied for 0.3 seconds every 4 seconds. Early in the testing the monkey was compelled to sample both sides of the table. In each animal electrical stimulation of some specific points of septum or amygdala increased the time the animal spent on the stimulating side. The statistical significance of the results was of the order of 1-5 per cent level of confidence. Motor activity of the animals was not affected during the stimulations, nor were there gross disturbances of the electrical activity of the brain. Stimulation of one septal point in two monkeys and of one amygdaloid point in another monkey decreased the time the animals spent on the stimulating side. Electrical stimulation of other points did not modify the time the animal spent on either side of the testing table. It may be concluded that stimulation of some cerebral areas is attractive, while the stimulation of other points is unattractive for the animal. Neutral areas also exist.

3. Action of Hormones upon Brain Excitability. Previous methods of investigating the effects of hormones and other substances upon brain excitability were based on the study of seizures evoked by electricity applied to the scalp (electroshock) or by drugs (pentametrazol). In these methods the whole brain was considered as a unit. In the present investigation we used our method of implanted electrodes to explore in the unanesthetized monkey the excitability of different areas of the brain. We attempted to learn whether DOCA, cortisone, ACTH and changes in serotonin, induced by marsalid, had a preferential action upon the excitability of septum pellucidum, anterior and posterior hippocampus,

and premotor and motor cortex. Thresholds for minimal effects were not modified by administration of DOCA, cortisone or ACTH. Thresholds for motor convulsive effect of area 4 were increased by administration of desoxycorticosterone, as were the thresholds for electrical afterdischarges. Marsalid produced a spectacular and lasting increase in thresholds for electrical afterdischarges of anterior hippocampus, less effect on motor cortex, and no effect on the septal area and posterior hippocampus.

4. Evoking conditioned Fear by Electrical Stimulation of Subcortical Structures in the Monkey Brain. An assembly containing six electrodes was implanted in mesencephalic, diencephalic, and rhinencephalic structures in the brains of ten monkeys (Macaca mulatta) which had been trained to avoid shock to the feet. Electrical stimulation of some structures evoked a response identical to the response performed by the animal to avoid shock; in other structures it evoked an inhibitory response, in some other structures a motor effect, and in some structures no apparent response. Stimulation of the following structures elicited the conditioned fear response: medial nucleus of the amygdala and adjacent tissue in rhinal fissure, trigeminal nerve at the Gasserian ganglion, rostral part of the pons, medial part of the mesencephalon in the vicinity of the central gray, nucleus ventralis posteromedialis, external part of the nucleus ventralis posterolateralis of the thalamus, and external medullary lamina of the pallidum. Electrical stimulation of the following structures did not evoke the avoidance response: sensorimotor cortex, sensorimotor pathways, nucleus ventralis lateralis of the thalamus, pulvinar of the thalamus, substantia nigra, part of the tegmentum inferior to the central gray, anterior hippocampus, posterior portions of the amygdaloid nucleus, and the putamen. A great variety of motor effects affecting head, eyes, face, forelimbs, hindlimbs and the tail were evoked by stimulation. In some instances responses were inhibited by stimulation. The results suggest that fear may be induced by electrical stimulation of some structures .

which appear to be related to the limbic system. These results are interpreted as indicating that electrical stimulation of some subcortical structures elicits fear responses which may be adapted to external circumstances.

5. The Effect on Delayed Alternation Test Performance of Stimulating or Destroying Electrically Structures Within the Frontal Lobes of the Monkey's Brain. Multilead electrodes were implanted bilaterally within the frontal lobes of 14 monkeys (Macaca mulatta) which had been trained in delayed-alternation and visual discrimination problems. The effect on the performance of these tests was observed while structures within the frontal lobe were being electrically stimulated through the electrode leads. Later, the effect on the performance of these tests was observed during electrocoagulation of these structures in some animals, and after electrocoagulation in others. The structures stimulated and electrocoagulated were determined by microscopic examination of stained sections. Impairment of the delayed-alternation test but not other visual discrimination tests resulted from stimulation of small areas in the head of the caudate nucleus, and not from any other structure. Electrocoagulation of tissue in the head of the caudate nucleus, but not in any other structure, also impaired delayed-alternation performance. Changes in activity and gastrointestinal disturbances followed stimulation of caudate nucleus and putamen. Electrocoagulation of tissue in the caudate nucleus and in the putamen resulted in gastrointestinal disturbances which lasted for a few days, and in hyperactivity which persisted throughout the remaining life of the animal. The results of this study suggest that the dalayed-alternation deficit, changes in activity, and gastrointestinal disturbances which frequently follow prefrontal lobotomy or ablation of the frontal cortex and which are usually ascribed to damage to the cortical projections from the thalamus, are due instead to damage to the corpus striatum, particularly to the caudate nucleus and its cortical projections. The complicated relationships between the behavioral affects of stimulation and coagulation preclude an explanation in terms of any one cerebral process.

6. Motor Representation in the Frontal Sulci of the Cat. Cortex hidden within enclosed portions of the sulci cruciatus, coronalis and presylvius was stimulated electrically in 20 cats under Dial anesthesia by means of bipolar concentric electrodes directed stereotaxically to penetrate the frontal lobe millimeter by millimeter. hidden cortex forming the walls of these sulci in each hemisphere had a combined extent of more than 300 sq. mm., an area comparable to the surface extent of the frontal lobe of the cat. Throughout subsurface cortex there was an important and essentially continuous "sensorimotor" region from which discrete somatic motor movements could be evoked. Stimulation of the cortex within the cruciate sulcus yielded movements of the contralateral hind-limb, trunk and tail. There was a small region of forelimb representation in the anterior part of this sulcus; forelimb responses were also elicitable from the anterior part of sulcus coronalis. Within the sulcus presylvius there was an extensive motor representation of the anterior half of the animal: forelimb movements were evoked near the top; head and neck movements, face, vibrissae, eyelid and eye movements, jaw, tongue, pupillary and respiratory responses were evoked in succession as the orbital surface was reached. There were differences in representation within the opposing surfaces of each of these three sulci and each bank appeared to provide a series of motor representations which were continuous with those evoked on stimulation of the surface gyri.

7. Use of Intracerebral Electrodes to Evaluate Drugs that Act on the Central Nervous System. Direct exploration of the brain of unanesthetized animals before and after administration of drugs may give information about their selective pharmacological action upon cerebral structures. Multilead implanted electrodes in cats and monkeys were employed for this purpose. To study different aspects of brain excitability and differential action of drugs, the following tests have been developed: 1) threshold for minimal motor response; 2) threshold for local motor-convulsive effects; 3) recovery time of convulsive capacity;

4) threshold for electrical afterdischarges. In addition to these, spontaneous electrical activity of the brain and its modification by drugs were investigated. The following substances were studied: 14 per nt CO_2, 10 per cent O_2, atropine, diphenylhydantoin, phenobarbital, trimethadione, chlorpromazine, reserpine, lysergic acid diethylamide, and tubocurarine. Differential actions of some of these substances upon motor cortex, limbic structures, and thalamus were described in this paper. As clinical application of experimental data it is suggested that knowledge concerning the action of drugs upon different cerebral structures may lead to more specific treatment of the symptoms of epilepsy.

8. Electrical Activity after Stimulation and Electrocoagulation of the Human Frontal Lobe.

9. The Persistence of Electroencephalogram Effects of Pentothal.

10. Use of Intracerebral Electrodes in Human Patients.

11. Surface and Depth Electrography of the Frontal Lobes in Conscious Patients.

12. Behavioral Changes During Intracerebral Electrical Stimulation. In the group of papers, numbers 8 through 12, results of application of the implanted electrode technique to human patients is described, showing clinical use in some difficult cases of epilepsy. Tape recorded interviews of the patients were synchronized with recordings of electrical activity of the brain and with the electrical stimulations, permitting the study of correlations of expression of ideas, behavior, and electrical phenomena. Patterns of intracerebral electrical activity were described and classified. Information concerning epileptic mechanisms showed constancy of temporal and spatial spread of spontaneous and evoked afterdischarges. Fear, hallucinations, déjà vu, and pleasure were repeatedly evoked by cerebral stimulation of specific areas.

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13. Respiratory Effects Evoked in the Awake Monkey by Brainstem and Cerebellar Stimulation. In 8 monkeys multilead electrodes were implanted in the cerebellum and brainstem. Stimulation of the nuclear structures in the cerebellum resulted in marked respiratory effects, mainly an increase in inspiratory amplitude. Possible mechanisms and roles were discussed. A decrease in inspiratory amplitude was obtained by electrical stimulation around the solitary tract and ventrolateral reticular substance. Increase in inspiratory amplitude was observed after electrical stimulation dorsal to the midportion of the inferior olive. The animals tolerated the presence of the electrodes well for periods up to 97 days. No changes in their respiratory pattern or behavior could be attributed to the presence of the electrodes. The histological reaction about the electrodes was studied, described and discussed in detail.

14. Chronic Emplacement of Intracerebral Electrodes. Methods used for chronic emplacement of intracranial electrodes, including remote control techniques, were briefly discussed. Construction of plate and needle multilead electrodes and surgery for their implantation were described. After months of implantation plate electrodes produced a small impression on the brain surface, with a slight glial reaction but no modification of neurons. A needle track after three months of implantation showed a central area, a limitant capsule, and the area of edema and partial demyelinization which is the transition to normal tissue. Histological elements and structure of needle track were described. Shape of the waves, voltage and amperage of electrical stimulation required monitoring during stimulation because they could be affected by tissue impedance. A few electrical stimulations repeated daily for months did not seem to produce permanent anatomical or functional modifications as evidenced by a) lack of local histological changes in stimulated areas; b) constancy of evoked effects; c) constancy of thresholds, with the exception of some limbic structures; d) constancy

of spontaneous electrical activity; e) constancy of evoked afterdischarges. On the other hand, half a second stimulation repeated every five seconds for one hour daily could produce lasting behavioral and electrical manifestations. Recordings of electrical activity may be considered spontaneous manifestations with negligible lesional disturbance. Electrical stimulation of some areas, such as septum, may produce a minor local electrical disturbance with very marked afterdischarge in remote areas, such as anterior hippocampus. Cerebral structures were electrically stimulated during psychological testing of animals. In this way positive and negative reinforcement has been shown. Discrete cerebral areas were electrocoagulated during performance of tests. Immediate effects of brain destruction were thus studied. In group behavior studies chronic stimulation of the brain induced a lasting increase of playful and contactual activities. Different tests to study the pharmacological sensitivity of the central nervous system have been developed, and differential action of drugs thus tested.

15. Brain Stimulation in the Monkey: Technique and Results. This is a 16 mm. sound, colored moving picture describing how permanent implantation of multilead electrodes in the brain permits study of cerebral function in awake animals. Materials and technique used in construction of surface and depth electrodes are shown. Presence of electrodes in the monkey's head apparently does not disturb its behavior. Responses demonstrated are: 1) motor effects: stimulation of area 4 evokes extension of contralateral arm and contralateral rotation of the body. 2) Sensory effects: the monkey scratches its face at each stimulation of the vicinity of the red nucleus. 3) Autonomic effects: coughing, gagging and vomiting are evoked by medullary stimulation; eye movements and nystagmus by tectal area stimulation. 4) Food intake: food ingestion stops and food is rejected when the neighborhood of the head of the caudate nucleus is stimulated. 5) Conditioning and pain inhibited: a monkey is trained to approach a light to avoid electric shock to the feet; stimulation of septal area inhibits response

to both light and shock. 6) Recording of electrical activity: movements of the monkey and simultaneous electrical activity of septal area, motor cortex, and anterior and posterior hippocampus are shown in the film. Stimulation of anterior hippocampus produced automatisms and electrical afterdischarges affecting anterior and posterior hippocampus and septal area, but not motor cortex. Stimulation of motor cortex evokes a motor and electrical seizure, first observable in motor area and later in hippocampus. Independence of motor cortex and hippocampus is thus demonstrated.

16. Electroencephalography of the Deeper Cell Masses of the Brain. This is a chapter in the book "Atlas of the Human Brain" by Bailey and Schaltenbrandt, to be published simultaneously in English and German.

17. Intracerebral Electrodes: Use in Physiology, Pharmacology and Psychology. This is an exhibit at the 1957 Annual Meeting of the Federation of American Societies for Experimental Biology, to be held in Chicago in April, 1957, and will show: 1) examples of somatic, autonomic and behavioral responses by cerebral stimulation; 2) site of action of cerebral stimulants and depressants; 3) transistor stimulator for wireless excitation of the brain; 4) study of social behavior by time-lapse photography; 5) epileptic mechanisms in human beings.

PLANS FOR FUTURE:

Immediate

1. Study of epilept c mechanisms will continue and will deal mainly with occipital cortex, motor cortex, premotor area, frontal lobes, limbic system, thalamus and brainstem.

2. The study of the site of action of drugs which affect the central nervous system will continue.

3. We already have considerable information concerning group behavior in monkeys recorded by time-lapse photography. The effect of remote-controlled

cerebral stimulation on group behavior will be studied.

Long Range

To develop the immediate program described above will take several years and therefore includes the long range plan. Clinical application of the technique of implanted electrodes to humans will also be carried on.

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